PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of a prospective, monocentric phase I/II feasibility study investigating the safety of multimodality treatment with a combination of intraoperative Chemotherapy and surgical Resection in locally confined or borderline resectable pancreatic cancer: The combiCaRe study
AUTHORS	Roth, Susanne; Springfeld, Christoph; Diener, M. K.; Tjaden, Christine; Knebel, Phillip; Klaiber, Ulla; Michalski, Christoph; Mieth, Markus; Jager, Dirk; Buchler, Markus W.; Thilo, Hackert

VERSION 1 – REVIEW

REVIEWER	Knut Jørgen Labori Oslo University Hospital, Norway
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	Roth et al present a study protocol for a prospective, monocentric phase I/II feasibility study investigating the safety of multimodality treatment with a combination of intraoperative chemotherapy and surgical resection in locally confined or borderline resectable pancreatic cancer. The study group state in the Introduction section that surgical manipulation of the tumour during pancreatic resection leads to dissemination of pancreatic cancer cells potentially founding the seeds for future metastases and local recurrence. Accordingly, perioperative systemic chemotherapy may reduce recurrence and thereby increase long-term survival by targeting intraoperatively shed cells as well as pre-existing micrometastases. The Introduction section nicely specifies the reasons for conducting the study in light of current knowledge. All relevant parts of a study protocol (rationale, study goals and objectives, study design, methodology, safety considerations, follow up, data management and statistical analysis, dissemination of results and publication) are adequately addressed in the manuscript. My comments are minor: 1) One of the inclusion criterias is histologically or cytologically proven pancreatic ductal adenocarcinoma. How will the sample be taken, by endoscopic ultrasound or percutaneously? Most studies would exclude patients who had undergone percútaneous cytology/biopsy. 2) In the presence of a solid mass suspicious for malignancy, consensus has been reached that biopsy proof is not required before proceeding with resection (HJ Asbun et al, Surgery 2014,

	155;5, 887-92). Confirmation of malignancy, however, is mandatory for patients with borderline resectable disease to be treated with neoadjuvant therapy before exploration for resection. The fact that patients needs a biopsy procedure in this trial should be included in the flow chart. 3) One of the exclusion criterias is abnormal hepatic function as defined by a total bilirubin level > 1.5 x the upper limit of normal (ULN), unless the patient has extrahepatic cholestasis due to pancreatic cancer. Does this mean that a patients with bilirubin 200 umol/l at the day of surgery due to biliary obstruction caused by the tumour will be included in the study, or does all patients have to undergo preoperative biliary stenting in order to receive intraoperative chemotherapy? If yes, the need for preoperative biliary stenting should be included in the flowchart. 4) Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants). Which variants are included? 5) (Partial) pancreaticoduodenectomy will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Does the procedure include non-touch pancreatoduodenectomy in that the tumor is not manipulated before the vascular and lymphatic drainage vessels are completely isolated? Reference 45 compared six patients undergoing PD with non-touch technique and six patients undergoing standard PD. Circulating tumor cells (CTCs) were measured from portal vein blood samples. Prior to resection of the pancreatic head, there was no difference in the number of CTCs between the 2 groups. Following resection, an increase in the number of CTCs was seen in 5 of 6 patients (83%) in the ST-PD group but 0 of 6 patients in the NT-PD group (P = .003) The study sample was small in that study, but is it a possibility that surgical technique has greater impact on intraoperatively shed cells than perioperative chemotherapy, and has this been considered in the current study? 7) How will portal venous blood and bone marrow be sampled? Are there any risks associated with these to these two procedures for the patients? 8) Why are no patient reported outcome (PRO) measures included in the protocol? 9) Page 6 Line 42: CTCs will be quantified, molecularly and functionally analysed in the systemic circulation and portal venous blood before, during and after pancreatic cancer resection. Will portal venous blood be sampled before and after pancreatic resection?

REVIEWER	Mitsugi Shimoda Tokyo Medical University, Ibaraki Medical center, Japan
REVIEW RETURNED	17-Feb-2019

GENERAL COMMENTS	Nothing in particular. I am looking forward to seeing the results as soon as possible.

REVIEWER	Ryan Merkow Northwestern University, Chicago, IL, USA
REVIEW RETURNED	04-May-2019

GENERAL COMMENTS	The authors present a well written and thoughtful proposed phase I/II study evaluating the role of intraoperative chemotherapy during pancreaticoduodenectomy. They should be applauded for pursing this study. As described, there is evidence to suggest CTCs increase during surgery, and this study aims to reduce the downstream consequences by treating potential intraoperative dissemination. The background and rationale is very clearly described. My minor suggestions include reporting available data supporting this treatment strategy, such as animal / preclinical studies. Other than just referencing the HIPEC literature, I recommend expanding on the safety of this therapy in more detail.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

We thank the reviewer for his careful and positive evaluation of our manuscript and for his helpful criticisms. We provide the following answers to his specific questions:

1) One of the inclusion criterias is histologically or cytologically proven pancreatic ductal adenocarcinoma. How will the sample be taken, by endoscopic ultrasound or percutaneously? Most studies would exclude patients who had undergone percutaneous cytology/biopsy.

Pancreatic biopsies will mostly be taken by endoscopic ultrasound if patients present primarily in our institution as a standard, yet patients who have undergone percutaneous biopsy before referral won't be excluded.

2) In the presence of a solid mass suspicious for malignancy, consensus has been reached that biopsy proof is not required before proceeding with resection (HJ Asbun et al, Surgery 2014, 155;5, 887-92). Confirmation of malignancy, however, is mandatory for patients with borderline resectable disease to be treated with neoadjuvant therapy before exploration for resection. The fact that patients need a biopsy procedure in this trial should be included in the flow chart.

We have revised the flow chart accordingly.

3) One of the exclusion criterias is abnormal hepatic function as defined by a total bilirubin level > 1.5 x the upper limit of normal (ULN), unless the patient has extrahepatic cholestasis due to pancreatic cancer. Does this mean that a patients with bilirubin 200 umol/l at the day of surgery due to biliary obstruction caused by the tumour will be included in the study, or does all patients have to undergo preoperative biliary stenting in order to receive intraoperative chemotherapy? If yes, the need for preoperative biliary stenting should be included in the flowchart.

If the extrahepatic cholestasis is due to the compressive nature of the tumor, patients with total bilirubin levels up to about 15 mg/dl (i.e. 256 umol/l) at the day of surgery will be included in the study without prior biliary stenting.

4) Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants). Which variants are included?

Since precise histopathological diagnosis of pancreatic ductal adenocarcinoma variants based on biopsy specimen is sometimes difficult due to sample limitations, variants including tubular adenocarcinoma, adenosquamous carcinoma, medullary carcinoma, hepatoid carcinoma, or undifferentiated carcinoma might be included.

Colloid carcinoma, signet ring cell carcinoma and undifferentiated carcinoma with osteoclastlike giant cells are usually distinguishable based on tumor biopsies and thus unlikely to be included in the study.

5) (Partial) pancreaticoduodenectomy will be performed according to the standards of care in the Department of Surgery at Heidelberg University Hospital. Does the procedure include non-touch pancreatoduodenectomy in that the tumor is not manipulated before the vascular and lymphatic drainage vessels are completely isolated? Reference 45 compared six patients undergoing PD with non-touch technique and six patients undergoing standard PD. Circulating tumor cells (CTCs) were measured from portal vein blood samples. Prior to resection of the pancreatic head, there was no difference in the number of CTCs between the 2 groups. Following resection, an increase in the number of CTCs was seen in 5 of 6 patients (83%) in the ST-PD group but 0 of 6 patients in the NT-PD group (P = .003) The study sample was small in that study, but is it a possibility that surgical technique has greater impact on intraoperatively shed cells than perioperative chemotherapy, and has this been considered in the current study?

Standard in our institution is not non-touch pancreatoduodenectomy. This is in accordance with the standard in most HPB surgery centers worldwide, including renown high-volume centers. The results of the mentioned study might be of interest although they are limited by the very small sample size. It needs to be proven in lager patient cohorts whether a nontouch pancreatic resection technique actually reduces intraoperative tumor cell dissemination. Preexisting micrometastasis at the time of surgery and local recurrence due to peripancreatic tumor cell spreading, which might be targeted by perioperative chemotherapy, won't be biased by the planned surgical procedure, as this is the same in all patients and – in contrast – introducing a new "non-touch" technique instead of the established standard would limit comparability.

7) How will portal venous blood and bone marrow be sampled? Are there any risks associated with these two procedures for the patients?

Bone marrow will be sampled by standard aspiration using a hollow needle from the iliac crests. Risks include excessive bleeding, infection, or discomfort at the biopsy site. Portal venous blood will be drawn by puncture with a 20 G needle. Potential risks include bleeding from the puncture site. In prior studies in our institution, both techniques have been applied in larger patient cohorts without observing any relevant procedure-related complications.

8) Why are no patient reported outcome (PRO) measures included in the protocol?

The main focus of the present pilot study is on the safety and feasiblity of the combined treatment with peri-/intraoperative chemotherapy and surgical resection and not long-term outcomes. Close monitoring of treatment associated complications and side effects include frequent patient surveys regarding any discomfort.

9) Page 6 Line 42: CTCs will be quantified, molecularly and functionally analysed in the systemic circulation and portal venous blood before, during and after pancreatic cancer resection. Will portal venous blood be sampled before and after pancreatic resection?
Yes.

Reviewer: 2

We thank the reviewer for his endorsement of our study.

Reviewer: 3

We thank the reviewer for his very positive evaluation.

My minor suggestions include reporting available data supporting this treatment strategy, such as animal / preclinical studies. Other than just referencing the HIPEC literature, I recommend expanding on the safety of this therapy in more detail.

We have followed his advice and included further available data supporting our proposed treatment strategy and elaborate on the safety of this therapy. On pages 4-5 of our revised manuscript we now state:

“Subclinical metastasis might occur early during tumour development1, 2, but iatrogenic tumor cell dissemination as a result of tumour manipulation during surgery is also a relevant concern3, 4. There is evidence that cancer cells are continuously released from the primary tumour into the bloodstream and lymphatic system, and circulating tumour cells (CTCs) are further increased by standard pancreaticoduodenectomy4. Several studies have shown that high levels of CTCs are associated with tumor progression and poor prognosis in pancreatic cancer patients5, 6, 7. Since surgical manipulation of the tumour during pancreatic resection leads to dissemination of pancreatic cancer cells potentially founding the seeds for future metastases and local recurrence, perioperative systemic chemotherapy may reduce recurrence and thereby increase long-term survival by targeting intraoperatively shed cells as well as pre-existing micrometastases. Computational modeling of pancreatic cancer progression indicates that tumor cell growth inhibiting therapies earlier in the course of treatment are even more effective than upfront tumor resection1.”

“Cytoreductive surgery including multiorgan resection combined with HIPEC is a wellestablished treatment option for peritoneal carcinomatosis of several gastrointestinal tumour entities, and the operative risk of the procedure has been shown to be similar to any other major gastrointestinal surgery8, 9. Likewise, perioperative chemotherapy including pancreatic and hepatic arterial infusion of 5-FU up to one week prior to pancreatic cancer resection and restarted again one week after surgery seemed to be safe and contribute to survival10. Therefore, intraoperative systemic chemotherapy during pancreatic resections should be well tolerated.”

VERSION 2 – REVIEW

REVIEWER	Knut Jørgen Labori Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Norway
REVIEW RETURNED	05-Jun-2019

GENERAL COMMENTS	The authors have addressed all my comments given in the first review (Reviewer 1) in detail and satisfactorily. The manuscript is in my opinion ready for publication in BMJ Open.